IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

GILEAD SCIENCES, INC.,	)	CV-13-4057-BLF
PLAINTIFF,	)	SAN JOSE, CALIFORNIA
VS.	)	MARCH 27, 2015
MERCK & CO, INC., ET AL,	)	PAGES 1-52
DEFENDANT.	)	

TRANSCRIPT OF PROCEEDINGS
BEFORE THE HONORABLE BETH LABSON FREEMAN
UNITED STATES DISTRICT JUDGE

A P P E A R A N C E S:

FOR THE PLAINTIFF: FISH & RICHARDSON PC
BY: DOUGLAS MCCANN
222 DELAWARE AVE, 17TH FL
WILMINGTON, DE 19801

FOR THE DEFENDANT: HUGHES HUBBARD & REED, LLP
BY: STEPHEN RABINOWITZ
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APPEARANCES CONTINUED ON THE NEXT PAGE

OFFICIAL COURT REPORTER: SUMMER FISHER, CSR, CRR
CERTIFICATE NUMBER 13185

PROCEEDINGS RECORDED BY MECHANICAL STENOGRAPHY
TRANSCRIPT PRODUCED WITH COMPUTER

FOR THE PLAINTIFF:	FISH & RICHARDSON, PC BY: JOHN FARRELL RACHEL SANCHEZ 500 ARGUELLO STREET, STE 500 REDWOOD CITY, CA 94063
ALSO PRESENT: GILEAD	JAMIE LYNCH KATHERINE RICE
FOR THE DEFENDANT:	DURIE TANGRI, LLP BY: LAURA MILLER 217 LEIDESDORFF STREET SAN FRANCISCO, CA 94111
ALSO PRESENT: ISIS	JASON FERRONE

SAN JOSE, CALIFORNIA MARCH 27, 2015

P R O C E E D I N G S

(WHEREUPON, COURT CONVENED AND THE FOLLOWING PROCEEDINGS WERE HELD:)

THE CLERK: CALLING CV-13-4057-BLF. CALLING CASE GILEAD SCIENCES, INC. V. MERCK & CO., ET AL.

COUNSEL, PLEASE COME FORWARD AND STATE YOUR APPEARANCES.

MR. RABINOWITZ: YOUR HONOR, STEPHEN RABINOWITZ, HUGHES, HUBBARD & REED, ON BEHALF OF THE DEFENDANTS AND COUNTER CLAIMANTS MERCK AND ISIS PHARMACEUTICALS.

THE COURT: GOOD MORNING.

MS. BROWN: WANDA FRENCH BROWN, HUGHES, HUBBARD & REED, ON BEHALF OF DEFENDANTS.

MS. MILLER: LAURA MILLER DURIE TANGRI, ON BEHALF OF DEFENDANTS.

MR. RABINOWITZ: YOUR HONOR, WE ARE ACCOMPANIED BY JASON FERRONE WHO IS VICE PRESIDENT OF PATENTS FOR ISIS PHARMACEUTICALS.

MR. MCCANN: GOOD MORNING, YOUR HONOR.

DOUG MCCANN, FISH RICHARDSON, ON BEHALF OF PLAINTIFF GILEAD SCIENCES.

MS. SANCHEZ: RACHEL SANCHEZ ON BEHALF OF THE PLAINTIFF, GILEAD SCIENCES.

MR. FARRELL: GOOD MORNING, YOUR HONOR. JOHN FARRELL.

MR. MCCANN: AND YOUR HONOR, ALSO WITH US IS JAMIE LYNCH AND KATHERINE RICE FROM GILEAD.

THE COURT: GOOD MORNING.

ALL RIGHT. WELL, THANK YOU FOR MAKING YOUR WAY TO OUR COURTHOUSE THIS MORNING.

THIS MORNING WE HAVE A LIMITED SCOPE. YOU ARE GOING TO TEACH ME ABOUT THIS PATENT AND THE SCOPE, THE CLAIMS CONSTRUCTION HAS NARROWED SIGNIFICANTLY TO INVOLVE ONLY THE '499 PATENT, AND SO THAT WILL BE OF ASSISTANCE.

AND MAYBE YOU CAN JUST GIVE ME A SENSE OF HOW YOU WANT TO PROCEED TODAY.

MR. RABINOWITZ: YOUR HONOR, WE DISCUSSED THIS AND WE AGREED THAT THE PRESENTATIONS WOULD BE IN THE SAME ORDER AS THE BRIEFING, SO THAT THE PATENT OWNER MERCK AND ISIS WILL PRESENT THEIR TUTORIAL FIRST.

THE COURT: GOOD. AND I THINK THAT ALWAYS MAKES SENSE TO LET THE PATENT OWNER HAVE THE FIRST WORD.

SO THAT'S FINE. AND OF COURSE I HAVE YOUR -- THE PAPERS THAT WE WILL BE WORKING ON NEXT WEEK FOR THE ACTUAL CLAIMS CONSTRUCTION HEARING, SO THAT HAS GIVEN ME A LITTLE INSIGHT INTO WHERE WE ARE ULTIMATELY GOING.

I PROBABLY WILL ASK YOU SOME QUESTIONS TODAY TO HELP ME UNDERSTAND WHERE I THINK WE ARE GOING NEXT WEEK AND SO I WILL ASK FOR THAT.

BEFORE WE GET STARTED, LET ME TELL YOU I HAVE A JURY

DELIBERATING AND I ANTICIPATE BEING INTERRUPTED, AND IT'S JUST THE WAY IT WILL HAVE TO BE. SO I APPRECIATE YOUR INDULGENCE IN THAT, BUT THEY DO TAKE PRIORITY.

AND SO WE MAY -- I WOULD ACTUALLY ANTICIPATE AT SOME POINT THIS MORNING WE MAY HAVE A LENGTHY INTERRUPTION OF UP TO 30 MINUTES BECAUSE I THINK THEY ARE FINISHING UP THEIR WORK.

SO THANK YOU FOR THAT. AND SO I THINK WE WILL JUST START THEN WITH MERCK'S PRESENTATION AND THEN -- AND TIMING ON IT, HOW MUCH TIME DO YOU EACH THINK YOU WILL BE TAKING?

MR. RABINOWITZ: YOUR HONOR, OUR PRESENTATION IS QUITE SHORT, PROBABLY 15 MINUTES AT THE MOST, MAYBE 20.

THE COURT: THAT SOUNDS GREAT. IT SOUNDS LIKE A LECTURE IN COLLEGE THEN.

MR. RABINOWITZ: AND IN FACT, IT'S FOCUSED ON THE ONE DISPUTED TERM THAT REMAINS, "ADMINISTERING" AS USED IN THE SPECIFICATION AND CLAIMS OF THE '499 PATENT.

THE COURT: GOOD.

MR. RABINOWITZ: AND IT'S FOCUSED ON THE SCIENTIFIC BACKGROUND PRINCIPLES THAT FORM THE CONSTRUCTION OF THAT TERM AND WILL BE PRESENTED BY DR. JAMES WUEST, PROFESSOR OF CHEMISTRY AT THE USC MONTREAL.

THE COURT: GOOD. ALL RIGHT, THANK YOU.

MR. MCCANN: OURS WOULD BE MORE LIKE 35 MINUTES, YOUR HONOR.

THE APPROACH WE TOOK WAS TO PROVIDE THE COURT SOMETHING

OF A GLOSSARY, BOTH FOR THE MARKMAN HEARING COMING UP BUT ALSO THE SCIENCE BACKGROUND GENERALLY ABOUT THE DISEASE AND THE WAY THE DISEASE IS TREATED WITH THESE PARTICULAR TYPES OF MOLECULES.

SO NOT AS FOCUSED AS MERCK'S, BUT I THINK -- OUR HOPE WILL ALSO BE THAT IT'S HELPFUL TO THE COURT IN GIVING YOU SOMETHING YOU CAN REFER BACK TO FROM TIME TO TIME AS THE CASE PROCEEDS, NOT JUST NEXT WEEK, BUT GOING FORWARD.

THE COURT: ALL RIGHT. AND I DID GET MERCK'S -- I HAVE BOTH OF YOURS NOW. I FIND BOTH OF THESE TO BE VERY HELPFUL AFTERWARDS AND SO THANK YOU FOR PREPARING THOSE.

ALL RIGHT. I GUESS WE WILL START THEN. WE WILL JUST GET RIGHT DOWN TO WORK HERE.

THE COURT: AND THANK YOU FOR COMING UP TO THE PODIUM, I DO APPRECIATE THAT. IT'S NICE NOT TO HAVE TO LOOK FAR ACROSS THE ROOM FOR YOU.

DR. WUEST: THANK YOU VERY MUCH, YOUR HONOR.

MY BACKGROUND IS IN CHEMISTRY AND MEDICINAL CHEMISTRY. I RECEIVED A PHD FROM HARVARD IN 1973 IN ORGANIC CHEMISTRY. SUBSEQUENTLY I WORKED AS A RESEARCHER AT NORTHERN MEDICAL SCHOOL IN THE AREA OF PHARMACOLOGY.

THROUGH MY TRAINING AND MY SUBSEQUENT INDEPENDENT RESEARCH I'VE DEVELOPED A BROAD FAMILIARITY WITH SUBJECTS RELATED TO SCIENCE AND THE TECHNOLOGY UNDERLYING THE PATENTS THAT ARE IN DISPUTE.

I CONTINUE TO BE AN ACTIVE RESEARCHER AND A TEACHER. I TEACH THE UNDERGRADUATE AND GRADUATE LEVELS. I HAVE BEEN TEACHING FOR MORE THAN 40 YEARS.

I ALSO SERVE AS A MENTOR FOR UNDERGRADUATE, GRADUATE STUDENTS AND POST DOCTORAL FELLOWS, SO I HAVE A DETAILED UNDERSTANDING OF WHAT A PERSON WITH ADVANCED TRAINING IN THE FIELDS OF ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY KNOWS.

THE COURT: AND WHAT IS OUR TIME FRAME FOR THIS PATENT?

MR. RABINOWITZ: YOUR HONOR, JANUARY 18TH, 2002.

THE COURT: 2002.

SO YOU ALSO HAVE EXPERIENCE WITH ONE SKILLED IN THE ART IN 2002.

DR. WUEST: I WAS TEACHING AND DOING RESEARCH AT THAT POINT, SO I UNDERSTAND WHAT THE LEVEL OF UNDERSTANDING OF A PERSON IN THESE AREAS OF SCIENCE WAS AT THAT TIME, AND IS NOW, AND IN FACT WAS A LONG TIME BEFORE THAT.

THE COURT: GOOD. THANK YOU SO MUCH.

DR. WUEST: SO WHAT I HAVE BEEN ASKED TO DO TODAY IS GIVE YOU A COLLEGE-LEVEL PRESENTATION OF BASIC SCIENTIFIC PRINCIPLES THAT UNDERLIE THE PATENTS THAT ARE IN DISPUTE.

AND IN PARTICULAR, I UNDERSTAND THAT THE COURT NEEDS TO DEVELOP AN UNDERSTANDING OF THE TERM "ADMINISTERING" WHICH APPEARS AT DIFFERENT POINTS IN THE '499 PATENT AND THE '712 PATENT.

AND ON THE SLIDE I HAVE SHOWN YOU HERE, I HAVE TAKEN A PHRASE THAT APPEARS FROM THE DISCLOSURE OF THE '499 PATENT. IT'S A SENTENCE THAT APPEARS IN COLUMN 32. AND THAT SENTENCE IS HIGHLIGHTED HERE.

THE TERMS "ADMINISTRATION OF" AND "ADMINISTERING A" COMPOUND SHOULD BE UNDERSTOOD TO MEAN PROVIDING A COMPOUND OF THE INVENTION OR A PRODRUG OF A COMPOUND OF THE INVENTION TO THE INDIVIDUAL IN NEED.

SO MY MORE SPECIFIC OBJECTIVE TODAY IS TO PROVIDE THE COURT WITH AN UNDERSTANDING OF THE UNDERLYING SCIENCE THAT WILL ENABLE THE COURT TO COME TO A DECISION ABOUT HOW THIS PHRASE WOULD BE UNDERSTOOD BY A PERSON OF ADVANCED SKILLS IN THE AREA OF ORGANIC CHEMISTRY, MEDICINAL CHEMISTRY.

SO TO DO THAT I WILL NEED TO INTRODUCE CONCEPTS RELATED TO FOUR AREAS OF SCIENCE. AND THOSE ARE THE CONCEPTS OF A COMPOUND, THE CONCEPT OF METABOLISM, THE CONCEPT OF A DRUG AND THE CONCEPT OF A PRODRUG.

AND I WILL SIMPLY GO THROUGH THOSE FOUR TERMS AND PROVIDE AN UNDERSTANDING OF HOW THOSE TERMS ARE UNDERSTOOD BY PERSONS WHO ARE TRAINED IN THESE AREAS.

A COMPOUND IS A SUBSTANCE THAT CONSISTS OF TWO OR MORE CHEMICAL ELEMENTS IN UNION. AND WHEN I SAY "UNION" I INDICATE WHAT A CHEMIST WOULD MORE TECHNICALLY CALL A CHEMICAL BOND.

A SIMPLE EXAMPLE OF A COMPOUND IS WATER WHERE TWO ATOMS OF THE ELEMENT, HYDROGEN, ARE IN UNION WITH AN ATOM OF OXYGEN.

THAT IS TO SAY TWO ATOMS OF HYDROGEN ARE BONDED TO AN ATOM OF OXYGEN TO CREATE A CHEMICAL COMPOUND.

ONE OF THE THINGS THAT MAKES THE SUBJECT OF CHEMISTRY POWERFUL AND BEAUTIFUL IS THE FACT THAT ELEMENTS CAN BE COMBINED IN AN INFINITE NUMBER OF WAYS. AND BY USING THE ELEMENTS OF THE PERIODIC TABLE AND THE CONSTRUCTION OF A CHEMICAL UNION, IT'S POSSIBLE TO MAKE A STAGGERING RANGE OF COMPOUNDS BOTH SIMPLE AND COMPLEX.

AN EXAMPLE OF A COMPOUND THAT IS SOMEWHAT MORE COMPLEX THAN WATER IS THE COMPOUND GLUCOSE. GLUCOSE CAN BE REPRESENTED BY ITS CHEMICAL FORMULA WHICH IS SHOWN ON THE LEFT, C6, H12, O6. THAT IS A USEFUL REPRESENTATION BUT IT IS NOT UNIQUE BECAUSE DIFFERENT COMPOUNDS CAN HAVE THE SAME FORMULA BUT CAN HAVE DIFFERENT STRUCTURES.

SO A PERSON SKILLED IN THE AREA OF ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY WOULD UNDERSTAND THERE ARE CONVENTIONS FOR SPECIFYING THE STRUCTURE IN GREATER DETAIL.

IN THAT FORMALISM, THEY ARE REPRESENTED BY LINES. THAT IS TO SAY THE TWO ELEMENTS CONNECTED BY THAT LINE ARE CONSIDERED TO BE BONDED TOGETHER.

BECAUSE CARBON OCCUPIES A UNIQUE POSITION AMONG ELEMENTS BY BEING ABLE TO FORM COMPOUNDS WITH DIFFERENT ELEMENTS, IT SERVES AS THE BASIS FOR A PARTICULARLY LARGE RANGE OF CHEMICAL STRUCTURES. AND BECAUSE OF THE CENTRAL IMPORTANCE OF CARBON, THE CONVENTION IS NOT SPECIFICALLY REPRESENTED THE ATOMS OF

CARBON BY THE ELEMENT SYMBOL C, BUT TO UNDERSTAND THAT THEY ARE PRESENT AT THE INTERSECTION OF THE LINES UNLESS SOME OTHER ELEMENT IS SPECIFICALLY INDICATED TO BE THERE.

SO IF YOU LOOK AT THE PARTICULAR STRUCTURE OF GLUCOSE, YOU CAN SEE THAT, FOR EXAMPLE AT THIS PARTICULAR POSITION THERE'S AN INTERSECTION OF LINES. AND SOMEONE SKILLED IN THE ART, IN THE AREA OF ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY WOULD UNDERSTAND THAT AT THAT POSITION, IS AN UNSPECIFIED ATOM OF CARBON.

IF YOU LOOK THE AT FORMULA OF GLUCOSE, C6 H12 O6 AT THE LEFT AND YOU LOOK AT THE STRUCTURE ON THE RIGHT, YOU CAN SEE THE SIX ATOMS OF OXYGEN ARE PRESENT. AND YOU CAN SEE THAT THE SIX ATOMS OF CARBON ARE PRESENT, BUT THE ATOMS OF HYDROGEN DO NOT ADD UP TO 12. AND THAT'S BECAUSE AS ANOTHER CONVENTION IN THIS AREA, ATOMS OF HYDROGEN ARE UNDERSTOOD TO BE PRESENT ON ATOMS OF CARBON BECAUSE CARBON HAS THE CAPACITY TO FORM THE TOTAL OF FOUR BONDS.

SO IT'S UNDERSTOOD THAT THAT CAPACITY IS FILLED BY ADDING ATOMS OF HYDROGEN THAT ARE NOT EXPLICITLY INDICATED.

YOU WILL NOTICE IN THE STRUCTURE ON THE RIGHT THAT THE CONVENTION FOR DRAWING CHEMICAL STRUCTURES IS COMPLICATED BY THE USE OF SIMPLE LINES TO INDICATE BONDS.

THE COURT: OF WHAT KIND OF LINES?

DR. WUEST: SIMPLE STRAIGHT LINES TO INDICATE THE PRESENCE OF A BOND, AS WELL AS SOLID OR DASHED.

THIS IS BECAUSE COMPOUNDS ARE THREE DIMENSIONAL OBJECTS AND THEY NEED TO BE REPRESENTED FOR SIMPLICITY IN TWO DIMENSIONS. AND SO THE CONVENTION IS TO INDICATE THE THREE-DIMENSIONALITY OF THESE STRUCTURES AND INDICATE HOW THEY ARE ORIENTED IN SPACE BY THE CONVENTION OF USING WEDGES TO INDICAT ORIENTATION.

WHAT'S IMPORTANT IS TO NOTE THAT IN THE PATENTS THAT ARE IN DISPUTE THESE SAME FORMALISMS FOR DRAWING CHEMICAL STRUCTURES AND INDICATING CHEMICALS, YOU WILL NOTE THERE'S NOTHING DIFFERENT IN THE WAY THE COMPOUNDS ARE DESCRIBED IN THE DISCLOSURE OF THE PATENTS, AND IN THE CLAIMS OF THE PATENTS THE STRUCTURES ARE DRAWN.

AND THE STANDARD WAY OF TAKING TWO EXAMPLES FROM THE MANY EXAMPLES THAT ARE CITED IN THE PATENTS IN DISPUTE TO INDICATE THAT THIS IS SO IN ALL CASES, THE ATOMS ARE INDICATED IN CONVENTIONAL WAYS, AND THE ORIENTATION OF GROUPS IS INDICATED IN THAT WAY.

IT'S ALSO PERHAPS INTERESTING TO NOTE THAT THE STRUCTURES OF THE COMPOUNDS THAT ARE REPRESENTED BY STANDARD CHEMICAL DRAWINGS ARE ALSO REPRESENTED BY NAMES SO THAT CHEMISTS HAVE BOTH THE SYSTEM OF DRAWING STRUCTURES AND INDICATING BY SYSTEMATIC NAMES WHAT THOSE STRUCTURES ARE.

THE COURT: SO THIS STRUCTURE WOULD ALWAYS BE ASSOCIATED WITH THIS ARTICULATION.

DR. WUEST: EACH OF THESE TWO DESCRIPTIONS IS A

UNIQUE WAY OF DESCRIBING THE CHEMICAL STRUCTURE OF THE COMPOUND.

THE COURT: SO ONE SKILLED IN THE ART OF LOOKING AT THE DIAGRAM WOULD KNOW EXACTLY WHAT IT WAS.

DR. WUEST: PRECISELY.

THE COURT: AND THAT ARTICULATION IN WORDS IS NEVER REPRESENTED DIFFERENTLY THAN THIS DIAGRAM.

DR. WUEST: THERE ARE DIFFERENT WAYS OF EXPRESSING IT. YOU CAN SHOW EXPLICIT THREE-DIMENSIONAL REPRESENTATIONS OF THESE COMPOUNDS, BUT A PERSON WITH ADVANCED UNDERSTANDING OF ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY WOULD BE ABLE TO LOOK AT THESE STRUCTURES AND SEE THESE THREE-DIMENSIONAL ASPECTS.

THAT'S AN INTERESTING ASPECT OF THE FIELD, BUT REPRESENTATION IS A KEY IN THE FIELD OF ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY. THERE ARE DIFFERENT WAYS OF DOING IT, BUT I LOOK AT THE FIELD OF CHEMISTRY AS BEING HIGHLY VISUAL IN ITS TRANSFER OF INFORMATION. AND THAT WOULD BE PERCEIVED BY SOMEONE WITH THE TYPE OF TRAINING I'VE DESCRIBED IN ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY, IT WOULD BE POSSIBLE TO LOOK AT THESE STRUCTURES AND PERCEIVE WITHIN A SIGNIFICANT DEGREE WHAT THESE COMPOUNDS WOULD ACTUALLY LOOK LIKE IF YOU COULD SEE THEM AS THREE-DIMENSIONAL OBJECTS.

THE COURT: IT'S PARTICULARLY INACCESSIBLE FOR A LAYPERSON TO SEE DIAGRAMS THAT AREN'T EVEN RELATED TO ANOTHER LANGUAGE.

I JUST WANT TO BE CLEAR HOW THE GULF THAT -- I CAN HEAR YOU TELL ME THAT THESE WORDS WHICH I AM MORE FAMILIAR WITH, WHICH ISN'T SAYING MUCH, THAN THE DIAGRAM. AND YOU TELL ME THAT THIS IS THE VISUAL REPRESENTATION OF THAT ARTICULATION, AND I CAN LOOK AT IT AND I CAN MAKE ZERO SENSE OF IT.

SO TO THE EXTENT IT'S IMPORTANT FOR ME TO MAKE SENSE OF IT, WE'RE NOT -- YOU ARE AT TOO HIGH A LEVEL FOR ME. I DO NOT KNOW HOW IMPORTANT THAT IS, BUT THIS IS THE TIME FOR ME TO BE AS FORTHRIGHT AS I CAN BE SO THAT I CAN GET THE RIGHT RESPONSE.

DR. WUEST: THANK YOU, YOUR HONOR, FOR THESE PERCEPTIVE QUESTIONS ABOUT REPRESENTATION IN CHEMISTRY, BUT THE DETAILS ARE NOT IMPORTANT TODAY.

THE COURT: OKAY.

DR. WUEST: WHAT IS IMPORTANT IS THAT CHEMISTS USE THIS TYPE OF REPRESENTATION AND THEY UNDERSTAND IT.

THE COURT: I APPRECIATE THAT.

DR. WUEST: IN NORMAL LIFE WE ARE CONFRONTED WITH REPRESENTING THREE-DIMENSIONAL OBJECTS ON PIECES OF PAPER. ARCHITECTURE IS VERY MUCH LIKE THAT.

AND FOR A PERSON WITH AN UNDERSTANDING IN THE FIELD OF ORGANIC CHEMISTRY, THAT THREE-DIMENSIONALITY WOULD BE PERCEIVED IMMEDIATELY.

I DO NOT BELIEVE, YOUR HONOR, THAT YOU ARE GOING TO NEED TO BE ABLE TO DO THAT AT THIS POINT.

THE COURT: ALL RIGHT. THANK YOU.

DR. WUEST: SO I MOVE ON TO THE SECOND CONCEPT WHICH IS THE CONCEPT OF METABOLISM.

METABOLISM IS THE SET OF CHEMICAL PROCESSES THAT OCCUR WITHIN A LIVING ORGANISM IN ORDER TO MAINTAIN LIFE.

MANY OF THESE METABOLIC PROCESSES ARE EXTREMELY WELL UNDERSTOOD.

AN EXAMPLE THAT I THINK IS A GOOD ONE OF THE PROCESS OF METABOLISM IS THE TRANSFORMATION OF THE MOLECULE GLUCOSE, WHICH I HAVE ALREADY TALKED ABOUT, SHOWN HERE AT THE UPPER LEFT OF THE SLIDE, IN COMBINATION WITH MOLECULES OF OXYGEN, AND IS CONVERTED INTO SIX MOLECULES OF WATER, PER MOLECULE OF GLUCOSE AND SIX MOLECULES OF CARBON DIOXIDE.

THIS RELEASES A LARGE AMOUNT OF ENERGY, AND IN THE PROCESS OF METABOLISM, THIS ENERGY IS CAPTURED AND USED CHEMICALLY IN DIFFERENT WAYS TO SUSTAIN LIFE.

IT'S PERHAPS IMPORTANT TO MENTION THAT GLUCOSE CAN BE BURNED IN AIR AND THE SAME TRANSFORMATION WILL TAKE PLACE. BUT THE BEAUTY OF METABOLISM IS THAT THE REACTIONS THAT ARE CARRIED OUT IN THIS PROCESS ARE CARRIED UNDER A MUCH MILDER CONDITIONS USING WHAT A CHEMIST WOULD CALL A CATALYST, OR SPECIFICALLY IN THIS AREA, ENZYMES TO ALLOW THESE REACTIONS TO TAKE PLACE UNDER MUCH MILDER CONDITIONS. BUT THESE METABOLIC PROCESSES ARE WELL UNDERSTOOD IN THIS PARTICULAR CASE OF GLUCOSE.

THE THIRD CONCEPT THAT UNDERLIES THE PATENTS IN DISPUTE IS THE NOTION OF A DRUG. AND IN THE FIELD OF MEDICINAL

CHEMISTRY AND MEDICINE, A DRUG CAN BE CONSIDERED TO MEET THE FOLLOWING DEFINITION WHICH COMES FROM A STANDARD MEDICAL DICTIONARY.

A DRUG IS A THERAPEUTIC AGENT, ANY SUBSTANCE OTHER THAN FOOD, USED IN THE PREVENTION, DIAGNOSIS, ALLEVIATION, TREATMENT OR CURE OF DISEASE IN MAN AND ANIMAL.

THE FINAL CONCEPT THAT I NEED TO PRESENT IN THIS TUTORIAL ABOUT THE SCIENCE AND TECHNOLOGY THAT UNDERLIES THE PATENTS IN DISPUTE IS THE IDEA OF A PRODRUG.

A PRODRUG IS A MEDICATION ADMINISTERED IN A PHARMACOLOGICALLY INACTIVE FORM WHICH IS THEN CONVERTED INTO ACTIVE FORM BY NORMAL METABOLIC PROCESSES.

THIS IS THE DEFINITION ADOPTED FROM WIKIPEDIA. IT'S SOMETHING THAT REALLY REPRESENTS MY OWN UNDERSTANDING OF THIS PHENOMENON. IT'S TRUE THAT IN MANY CASES WIKIPEDIA DEFINITIONS DO NOT FIT EXACTLY THE WAY AN EXPERT IN THE FIELD WOULD UNDERSTAND IT, THIS IS A CASE WHERE IT FITS PERFECTLY.

NOW IT MAY BE POSSIBLE TO WONDER WHY SOMEONE WOULD CONSIDER USING A PRODRUG TO INTRODUCE A PHARMACOLOGICALLY ACTIVE COMPOUND. THERE ARE MANY WAYS OF DOING THAT. IT'S A STRATEGY THAT'S WELL DEVELOPED AND HAS BEEN UNDERSTOOD FOR DECADES.

THE ADVANTAGES ARE MULTI-FOLD. THEY CAN BE ADVANTAGES RELATED TO HOW THE COMPOUND IS DISTRIBUTED IN THE BODY, HOW EASY IT IS FOR COMPOUNDS TO PASS ACROSS MEMBRANES, IT MAY AVOID

PROBLEMS OF STABILITY THAT ARE ASSOCIATED WITH THE ACTIVE FORM, IT CAN BE SIMPLY BECAUSE OF TASTE, WHERE THE ACTIVE FORM IS PALATABLE AND THE PRODRUG FORM IS NOT.

SO I SAID THIS IS A CONCEPT THAT GOES BACK DECADES. ONE OF THE BEST AND EARLY EXAMPLES OF THIS STRATEGY OF PRODRUGS IS ASPIRIN ITSELF.

THE COURT: I DIDN'T KNOW THAT.

DR. WUEST: GOOD.

THE STRUCTURE OF ASPIRIN IS SHOWN HERE, IT'S CIRCLED AT THE LOWER LEFT, AND IT SERVES AS A PRODRUG FOR THE RELEASE OF THE COMPOUND SHOWN ON THE RIGHT WHICH IS SALICYLIC ACID.

SO THROUGH A METABOLIC PROCESS, THE ACETYL GROUP OF ASPIRIN, THE PRODRUG WHICH IS SHOWN HERE IN RED, IS CLEAVED OFF AND SALICYLIC ACID IS RELEASED.

THE COURT: SO SAY THAT AGAIN.

DR. WUEST: SO THERE IS A CHEMICAL GROUP PRESENT IN ASPIRIN THAT'S SHOWN IN RED IN THE STRUCTURE ON THE LEFT. AND THROUGH METABOLISM, THAT GROUP IS CLEAVED OFF. SO THIS IS THE KEY STEP IN THE USE OF A PRODRUG.

A PRODRUG NECESSARILY INVOLVES A METABOLIC STEP THAT IS DESIGNED TO RELEASE ACTIVE FORM. THAT IS WHAT IS HAPPENING HERE, IT'S A VERY SIMPLE EXAMPLE. THERE'S ONE STEP IN WHICH THE ACETYL GROUP IS CLEAVED OFF AND SALICYLIC ACID IS RELEASED.

SALICYLIC ACID IS A COMPOUND THAT HAS A PARTICULARLY UNPLEASANT TASTE. AND IF IT'S INTRODUCED DIRECTLY, IT ALSO

CAUSES SOMETIMES PSYCHEDELIA EFFECTS. SO THIS IS AN EXAMPLE OF WHY A PRODRUG STRATEGY --

THE COURT: IT'S VERY ASTRINGENT, ISN'T IT?

DR. WUEST: THE CHEMISTRY OF SALICYLIC ACID HAS A LONG HISTORY IN SCIENCE. IT INDIRECTLY COMES FROM THE BARK OF THE WILLOW, AND FOR MANY YEARS BEFORE PEOPLE UNDERSTOOD WHAT THE PRODRUG STRATEGY IS, PEOPLE RECOGNIZED THE ANALGESIC CAPACITIES.

THE COURT: SO LET ME ASK YOU A QUESTION ABOUT PRODRUG.

IF YOUR GOAL IS TO CREATE SALICYLIC ACID IN THE BODY THROUGH SOME METABOLIC PROCESS, ARE THERE THEORETICALLY A NUMBER OF DIFFERENT DISTINCT PRODRUGS THAT COULD BE, WE WILL USE "ADMINISTERED", MAYBE I SHOULDN'T, BUT THEY CAN BE USED OR INTRODUCED INTO THE BODY, THAT WILL METABOLIZE DIFFERENTLY TO REACH THE SAME RESULT.

DR. WUEST: THERE ARE A RANGE OF POSSIBILITIES. BUT I MENTIONED BEFORE THAT METABOLISM IN MANY AREAS IS UNDERSTOOD AND CAN BE STUDIED. AND IF THAT IS KNOWN, THEN A PERSON WITH ADVANCED SKILLS IN ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY CAN ANTICIPATE HOW THE COMPOUND WOULD BE METABOLIZED.

IN THE CASE OF ASPIRIN, THE CLEAVAGE, THE ACETYL GROUP WOULD BE SOMETHING YOU ANTICIPATE TO TAKE PLACE UNDER METABOLIC CONDITIONS.

YOU COULD REPLACE THE ACETYL GROUP BY SOMEWHAT RELATED

CHEMICAL GROUPS, THEREBY CREATING A RANGE OF POSSIBILITIES.

THE COURT: SO I GUESS WHAT I'M THINKING THEORETICALLY, BUT YOU HAVE TO TELL ME IF I'M OUTSIDE THE REALM OF REALITY, IF WE KNOW THAT ASPIRIN, WHEN INTRODUCED INTO THE BODY, WILL GO THROUGH THIS METABOLIC PROCESS TO CREATE THE SALICYLIC ACID, SO WE'VE GOT THAT PROCESS, IS IT POSSIBLE THAT A DIFFERENT PRODRUG WHEN INTRODUCED INTO THE BODY WILL ACTIVATE A DIFFERENT METABOLIC PROCESS, BUT BECAUSE OF A COMPOUND INTRODUCED INTO THE BODY AND THAT SEPARATE METABOLIC PROCESS END UP WITH THE SAME RESULTS?

DR. WUEST: YES, YOU COULD CHOOSE DIFFERENT METABOLIC PATHWAYS TO HELP DESIGN THE PRODRUG FORM THAT WOULD BE CONVERTED INTO THE ACTIVE FORM THROUGH DIFFERENT ROUTES.

THIS IS A CASE WHERE A PERSON WHO KNOWS THE FIELD OF ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY WOULD SEE THAT IT INVOLVES ISOLATION OF AN OXYGEN AND CLEAVAGE OF THAT GROUP THROUGH METABOLIC PROCESS.

MY PERSPECTIVE ON THIS FIELD IS THAT A VERY CONSIDERABLE EMPHASIS NEEDS TO BE PLACED ON THE IDENTITY OF THE ACTIVE FORM, BECAUSE REGARDLESS --

THE COURT: THE ACTIVE FORM BEING?

DR. WUEST: THE ACTIVE FORM BEING THE SALICYLIC ACID IN THIS EXAMPLE WITH ASPIRIN, BECAUSE NOTHING YOU PICK AS A PRECURSOR WILL DO YOU ANY GOOD UNLESS THROUGH METABOLIC TRANSFORMATIONS, IT'S CONVERTED INTO THAT PARTICULAR COMPOUND.

THE COURT: YES, THAT I UNDERSTAND. THIS IS OUR GOAL. WE HAVE ONE GOAL.

AND I'M JUST ASKING AND YOU'VE GIVEN ME THAT ANSWER. THERE THEORETICALLY COULD BE MANY PATHS TO THAT GOAL.

DR. WUEST: THEORETICALLY, YES. ASPIRIN IS PARTICULARLY EFFECTIVE FOR VARIOUS REASONS, BUT THERE WOULD BE OTHER CONCEIVABLE PRECURSORS OF THAT ACTIVE SALICYLIC ACID.

THE COURT: AND OTHERS MIGHT HAVE SIDE EFFECTS, THEY MIGHT NOT BE AS STABLE, THEY COULD HAVE LOTS OF THINGS THAT MAKE ASPIRIN THE BEST, BUT THERE COULD BE OTHERS.

DR. WUEST: I THINK THAT'S A FAIR UNDERSTANDING.

THE COURT: OKAY.

DR. WUEST: SO I THINK I DON'T NEED TO EXPLAIN THIS PARTICULAR PRESENTATION, BUT IT SIMPLY REEMPHASIZES THAT THE PRODRUG IS INTRODUCED, AND THEN THROUGH METABOLIC TRANSFORMATIONS IT IS CONVERTED INTO THE ACTIVE FORM, SALICYLIC ACID, WHICH FINDS ITSELF EVENTUALLY AT SITES WHERE IT DOES GOOD.

SO WE COME BACK TO THE SENTENCE THAT I MENTIONED EARLIER IN THIS TUTORIAL AS ONE THAT REPRESENTS THE AREA OF THE BASIC SCIENTIFIC PRINCIPLES I PRESENTED ARE NEEDED TO UNDERSTAND HOW SOMEONE WITH ADVANCED TRAINING IN ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY WOULD INTERPRET THIS SENTENCE.

AND I EMPHASIZE WHAT I SAID EARLIER THAT THE PRODRUG CONCEPT IS SOMETHING THAT CANNOT BE DIVORCED FROM METABOLISM.

IF YOU USE A PRODRUG STRATEGY, THEN NECESSARILY YOU ARE COUNTING ON METABOLIC PROCESSES TO CONVERT THAT COMPOUND INTO ACTIVE FORM.

SO WHEN THIS SENTENCE SAYS THAT A PRODRUG OF A COMPOUND, IT MEANS THAT FOR THAT SPECIFIC COMPOUND, THE PRODRUG FORM, WHATEVER IT IS, WILL BE CONVERTED METABOLICALLY INTO THAT SAME COMPOUND.

THE COURT: IS THE COMPOUND THE END RESULT?

DR. WUEST: THE COMPOUND, IN THIS PARTICULAR CASE, IS IN FACT THE ACTIVE FORM.

THE COURT: SO IT WOULD BE THE SALICYLIC ACID IN YOUR ASPIRIN.

DR. WUEST: THAT WOULD BE THE SALICYLIC ACID.

THE COURT: OKAY.

SO IN THIS PHRASE OR SENTENCE FROM THE PATENT, SO IF WE ARE PROVIDING A COMPOUND OF THE INVENTION, THAT IS SOMETHING THAT IS CREATED AND EXISTS BEFORE IT IS INTRODUCED INTO THE BODY; IS THAT WHAT THAT PHRASE IS, "A COMPOUND OF THE INVENTION"?

DR. WUEST: WELL, A COMPOUND OF THE INVENTION WOULD BE COMPOUNDS THAT ARE WITHIN THE SCOPE OF THE STRUCTURAL FORMULAE THAT WOULD BE IN THE CLAIMS OF THE PATENT IN DISPUTE.

THE COURT: SO LET ME BACK UP. LET'S JUST STICK WITH ASPIRIN.

WHEN THIS SAYS "PROVIDING A COMPOUND OF THE INVENTION",

WOULD THAT BE SALICYLIC ACID?

DR. WUEST: IN THIS CASE -- OKAY, I UNDERSTAND WHAT YOU'RE ASKING.

THE COURT: I'M JUST TRYING TO UNDERSTAND THE DIFFERENCE. BECAUSE THERE'S AN "OR" SO THERE ARE TWO DIFFERENT THINGS.

DR. WUEST: SO WHAT THIS MEANS IS WE WILL HYPOTHETICALLY CONSIDER ASPIRIN TO BE A COMPOUND OF AN INVENTION.

THE COURT: ASPIRIN IS THE COMPOUND.

DR. WUEST: SALICYLIC ACID IS THE COMPOUND OF THE INVENTION, YES.

THE COURT: THANK YOU. OKAY.

DR. WUEST: AND THE PRODRUG OF THAT WOULD, FOR EXAMPLE, BE ASPIRIN.

THE COURT: WOULD BE ASPIRIN.

AND SO THE COMPOUND OF THE INVENTION THEN PRESUMES THE PROCESS OF A PRODRUG INTRODUCED INTO THE BODY, METABOLIZING AND BECOMING SALICYLIC ACID?

DR. WUEST: THAT'S RIGHT.

THE POINT OF MY PRESENTATION, THE SCIENTIFIC FUNDAMENTALS IS TO INDICATE THAT THE IDEA OF PRODRUG CANNOT BE SEPARATED FROM THE IDEA OF METABOLISM.

AND THAT WHEN YOU SAY A PRODRUG OF A COMPOUND, YOU NECESSARILY MEAN THAT THAT SPECIFIC COMPOUND WILL BE FORMED

METABOLICALLY FROM THE PRODRUG FORM.

AND THAT'S WHY I INSISTED EARLIER ON THE IMPORTANCE OF RECOGNIZING THE ACTIVITY OF SALICYLIC ACID, BECAUSE ASPIRIN IS A PRODRUG FORM AND THE RELEASE OF THE ACTIVE SALICYLIC ACID NECESSARILY REQUIRES THE USE OF THE METABOLIC PROCESSES OF THE BODY.

THE COURT: AND SO AGAIN, JUST TRYING TO UNDERSTAND THIS PHRASE, SO THE FIRST PART, COMPOUND OF THE INVENTION, IS THE ULTIMATE ACTIVE FORM, THE SALICYLIC ACID. AND THE "OR" WOULD BE THE ASPIRIN ITSELF.

DR. WUEST: THAT'S RIGHT. YOU COULD CONCEIVABLY INTRODUCE SALICYLIC ACID DIRECTLY. AS I SAID, THAT WOULD HAVE --

THE COURT: THAT WOULD GIVE YOU A BIG STOMACH ACHE.

DR. WUEST: YOU WOULD NOT LIKE THE TASTE, YOU MIGHT HAVE RINGING IN YOUR EARS WHICH ARE AMONG THE SECONDARY EFFECTS OF TAKING SALICYLIC ACID.

THE COURT: WELL, THAT'S WHAT I'M TRYING TO DISTINGUISH HERE. AND I APOLOGIZE FOR HAVING SO LITTLE KNOWLEDGE, BUT I CAN UNDERSTAND THAT THE COMPOUND OF THE INVENTION COULD BE, AND THIS COMES UP IN THE BRIEFING, SOMETHING CREATED IN THE LAB. SO THAT HAS NOTHING TO DO WITH METABOLISM.

AND THAT'S -- YOU ARE SAYING THAT'S NOT WHAT IT IS. YOU ARE SAYING THE COMPOUND OF THE INVENTION IS IN FACT THE ENTIRE

PROCESS.

DR. WUEST: WELL, YOU HAVE TO REMEMBER THAT THE COMPOUND OF THE INVENTION WOULD NOT NECESSARILY HAVE TO BE A CONSTRUCTION IN THE LABORATORY, IT COULD BE A NATURAL PRODUCT THAT'S BEING USED FOR SOME PURPOSE THAT NO ONE HAD DISCOVERED BEFORE.

THE COURT: YES, I HEAR YOU THERE.

SO LET ME REPHRASE THAT. IS THE -- I'M TRYING TO UNDERSTAND THIS PHRASE TO UNDERSTAND WHETHER COMPOUND OF THE INVENTION IS SOMETHING THAT EXISTS WITHOUT METABOLISM.

AND THEN THE SECOND PART OR THE PRODRUG OF A COMPOUND OF THE INVENTION WHICH WOULD BE THE, SOMETHING THAT EXISTS BEFORE INTRODUCTION TO THE BODY AND IS DEPENDENT UPON METABOLISM TO BECOME SOMETHING ELSE.

THAT'S WHERE I'M CONFUSED ABOUT THIS. THERE ARE TWO SIDES TO THIS PHRASE, SO THESE THINGS ARE DIFFERENT FROM EACH OTHER.

DR. WUEST: I'M NOT SURE THAT I FOLLOWED YOUR QUESTION COMPLETELY.

THE COURT: I'M SORRY, I UNDERSTAND YOU ARE HEARING MY CONFUSION.

DR. WUEST: I WILL TAKE A STAB AT AN ANSWER.

THE COMPOUND OF THE INVENTION, I THINK I UNDERSTAND THAT TO BE A COMPOUND WITHIN THE SCOPE OF A STRUCTURAL FORMULAE IN THE PATENTS IN DISPUTE IN THIS PARTICULAR CASE.

THE COURT: WHICH UTILIZES METABOLISM.

DR. WUEST: WHICH COULD BE SALICYLIC ACID.

IN A SENSE, SALICYLIC ACID CAN BE USED AS AN EXAMPLE. SALICYLIC ACID ITSELF CAN BE CREATED IN THE LABORATORY OR IT, AND INDEED IT IS, IT'S ALSO CREATED METABOLICALLY BY THE WILLOW AND BY OTHER PLANTS, THERE ARE OTHER SOURCES IN NATURE.

THE COURT: BUT THIS INVENTION IS NOT ABOUT SALICYLIC ACID PRODUCED IN THE LABORATORY OR -- I MEAN, THAT'S OUR EXAMPLE.

DR. WUEST: A COMPOUND OF THE INVENTION IN THIS PARTICULAR CASE COULD BE SALICYLIC ACID DERIVED FROM NATURAL SOURCES BUT FINDING AN APPLICATION THAT NO ONE HAD UNDERSTOOD BEFORE.

I MEAN, ASPIRIN IS USED FOR IT'S ANALGESIC EFFECT, WHICH IS ULTIMATELY THAT OF THE ACTIVE SALICYLIC ACID FORM. SO THAT WOULD BE A COMPOUND OF THE INVENTION AND IT WOULD BE CREATED THROUGH METABOLIC PROCESS.

IT COULD ALSO BE SYNTHESIZED IN THE LABORATORY. IF THE PERSON WHO IS TRAINED IN ORGANIC CHEMISTRY OR MEDICINAL CHEMISTRY, THEY MAKE DISTINCTIONS BETWEEN THESE TWO WHEN IT'S APPROPRIATE, BUT IN THIS PARTICULAR CASE IT DOESN'T REALLY MATTER WHERE THE COMPOUND COMES FROM.

THE COURT: IN JUST DOING THE READING FROM THE PAPERS IT SEEMED THAT ONE OF THE PRIMARY BENEFITS OF USING A PRODRUG IS TO ENSURE THE, AS YOU SAY, THE STABILITY AND THE

EFFECTIVENESS OF THE ULTIMATE, I DON'T KNOW WHAT WE CALL IT, COMPOUND, THE ULTIMATE COMPOUND WHEN IT NEEDED TO DO GOOD FOR THE DISEASE THAT YOU'RE ATTACKING.

SO SALICYLIC ACID MAY EXIST OUTSIDE THE BODY, BUT IT'S COMPLETELY USELESS FOR THIS PURPOSE BECAUSE IN THE PROCESS OF GOING THROUGH THE METABOLIC FUNCTIONS OF THE BODY IT GETS BROKEN DOWN, DESTABILIZED OR WHATEVER MIGHT HAPPEN TO IT.

ISN'T THAT THE PURPOSE OF THE PRODRUG TO AVOID THE DEGRADATION OF THE COMPOUND IN THE METABOLIC PROCESS, BUT RATHER ACTIVATE THE METABOLIC PROCESS TO CREATE THE COMPOUND AT THE POINT AT WHICH IT CAN BE MOST EFFECTIVE?

DR. WUEST: THOSE ARE EXCELLENT QUESTIONS, BUT IT'S IMPORTANT TO KEEP IN MIND THAT THE PRODRUG FORM IS NOT THERAPEUTICALLY ACTIVE.

THE COURT: I UNDERSTAND THAT.

DR. WUEST: IT'S IN -- THE PRODRUG FORM IS NOT THERAPEUTICALLY ACTIVE TO THE DEGREE THAT THE DESIRED FORM THAT RESULTS FROM METABOLIC TRANSFORMATIONS WOULD BE ACTIVE. THE TRICK IS TO GET THE THERAPEUTICALLY ACTIVE FORM WHERE IT IS NEEDED, AND THE PRODRUG STRATEGY OFFERS ADVANTAGES OF VARIOUS TYPES.

IT MIGHT BE BENEFICIAL TO GO BEYOND THE CASE OF ASPIRIN AND SALICYLIC ACID TO A MORE RECENT AND PERTINENT EXAMPLE OF A PRODRUG, BECAUSE THAT WILL ACQUAINT THE COURT WITH THE RANGE OF POSSIBILITIES THAT CAN TAKE PLACE.

MAYBE I COULD GO ON AND MOVE TO THAT.

THE COURT: YES, PLEASE.

DR. WUEST: SO WHAT I SHOW ON THIS PARTICULAR SLIDE IS THE PARTICULAR CASE OF SOFOSBUVIR, WHICH IS THE COMPOUND SHOWN ON THE FAR LEFT.

THE PARTICULAR STRUCTURAL DRAWINGS I SHOW HERE HAVE BEEN TAKEN FROM PAGE 4 OF GILEAD'S CLAIM CONSTRUCTION BRIEF WHICH ACKNOWLEDGES THAT SOFOSBUVIR IS A PRODRUG IN THE SAME SENSE THAT ASPIRIN IS A PRODRUG OF SALICYLIC ACID.

AND IT IS CONVERTED BY METABOLIC STEPS INTO THE CORRESPONDING MONOPHOSPHATE SHOWN HERE, DIPHOSPHATE SHOWN HERE, AND FINALLY INTO THE PHYSIOLOGICALLY ACTIVE FORM THE TRIPHOSPHATE WHICH IS SHOWN ON THE RIGHT.

NOW ALL THREE OF THESE COMPOUNDS, THE MONOPHOSPHATE, THE DIPHOSPHATE AND THE TRIPHOSPHATE, ARE COMPOUNDS OF THE INVENTION IN THE SENSE THAT THEY LIE WITHIN THE SCOPE OF THE STRUCTURAL FORMULAE IN THE TWO PATENTS IN DISPUTE IN THEIR CLAIMS.

THE COURT: SO THE PORTION IN THE MIDDLE IN BLACK ARE TRANSITORY STAGES ON THE WAY OF WHAT YOU CALL THE DRUG?

DR. WUEST: I THINK THAT'S A GOOD WAY OF REPRESENTING IT, THEY HAPPEN TO BE COMPOUNDS OF THE INVENTION.

BUT IN THIS PARTICULAR CASE THE METABOLIC TRANSFORMATION OCCURS THROUGH MULTIPLE STEPS AS OPPOSED TO THE SINGLE STEP THAT TOOK PLACE IN THE CONVERSION OF SALICYLIC ACID, THE

CONVERSION OF ASPIRIN INTO SALICYLIC ACID.

BUT THIS IS A CASE IN WHICH METABOLIC PROCESSES CONVERT THE INITIAL MONOPHOSPHATE INTO A DIPHOSPHATE AND INTO THE TRIPHOSPHATE FORM.

THE COURT: SO IT ACTUALLY BECOMES MORE COMPLEX THROUGH METABOLISM, IS THAT ACCURATE?

DR. WUEST: WELL, IN THE CASE OF ASPIRIN BEING CONVERTED INTO SALICYLIC ACID, A GROUP IS CLEAVED OFF.

THE COURT: YES.

DR. WUEST: THIS IS A SIMILAR TRANSFORMATION OF A PRODRUG, AND IF YOU LOOK AT THE STRUCTURALS CAREFULLY YOU CAN SEE IN THE CONVERSION OF SOFOSBUVIR THROUGH METABOLISM, AND IT'S IN THE ACTIVE TRIPHOSPHATE FORM, A PORTION OF THE MOLECULE IS INDEED CLEAVED OFF.

THE COURT: I SEE, YES.

DR. WUEST: THEN SUBSEQUENTLY THE MOLECULE IS BUILT UP.

BUT IT'S IMPORTANT TO UNDERSTAND, AS I POINTED OUT BEFORE, THAT METABOLISM IN THE AREAS OF BIOLOGICAL CHEMISTRY IS UNDERSTOOD AND PEOPLE CAN ANTICIPATE HOW THESE METABOLIC CLEAVAGES AND BUILDING UP OF MORE COMPLEX STRUCTURES WOULD BE EXPECTED TO TAKE PLACE AND THEY CAN TAKE FULL ADVANTAGE OF THAT, AS LONG AS THEY KNOW WHERE THEY ARE GOING.

JUST AS IN THE CASE OF ASPIRIN BEING CONVERTED INTO SALICYLIC ACID. IF YOU DID NOT UNDERSTAND THAT SALICYLIC ACID

HAD AN ANALGESIC EFFECT, YOU WOULD BE ALL TOGETHER LOST. THERE ARE SOME OPTIONS FOR DECIDING WHAT PRODRUG FORM TO USE, BUT THE KEY IS TO UNDERSTAND THAT METABOLISM WILL DO CERTAIN THINGS IN A PREDICTABLE WAY. AND YOU CAN TAKE ADVANTAGE OF THAT TO INTRODUCE A PHYSIOLOGICALLY ACTIVE COMPOUND THROUGH A PRODRUG STRATEGY.

THE COURT: ALL RIGHT.

DR. WUEST: YOU CAN'T DIVORCE THE CONCEPT OF THE PRODRUG FROM METABOLISM.

THE COURT: OKAY.

DR. WUEST: MAY I GO ON THEN?

THE COURT: PLEASE.

DR. WUEST: THIS SUMMARIZES WHAT I PRESENTED ON THE EARLIER SLIDE, BUT WITH THE COURT'S PERMISSION, I WOULD LIKE TO SHOW A 15 SECONDS OF AN ANIMATION.

THE COURT: OKAY.

DR. WUEST: THAT WAS PART OF THE MATERIAL PROVIDED TO THE COURT AND TO COUNSEL FOR THE DEFENDANTS BY GILEAD THIS WEEK, ON WEDNESDAY, AND IT'S A NICE SUMMARY OF WHAT I'VE TRIED TO CONVEY FROM THESE.

THE COURT: IS THAT A COMPLIMENT?

MR. MCCANN: APPARENTLY, IT IS, YOUR HONOR.

DR. WUEST: SO MAY I PROCEED WITH THAT THEN?

THE COURT: PLEASE.

DR. WUEST: SO THIS IS 18 SECONDS.

(WHEREUPON, A VIDEO WAS PLAYED IN OPEN COURT.)

DR. WUEST: THAT'S FINE.

SO JUST FOR THE COURT'S UNDERSTANDING, THE COMPOUND WITH THE NAME GS FOLLOWED BY NUMBERS IS THE ACTIVE TRIPHOSPHATE FORM.

SO THIS SUMMARIZES THE CONCEPT THAT I'VE TRIED TO PRESENT, NAMELY THAT SOFOSBUVIR ACTS AS A PRODRUG FORM, IT IS CONVERTED INTO METABOLISM INTO THE ACTIVE TRIPHOSPHATE FORM WHICH I SHOWED EARLIER.

THE COURT: OKAY. THANK YOU SO MUCH. AND THANK YOU FOR INDULGING IN MY QUESTIONS.

DR. WUEST: OKAY. YOU'RE VERY WELCOME.

MR. MCCANN: MAY I PROCEED, YOUR HONOR?

THE COURT: YES, PLEASE.

MR. MCCANN: SO YOUR HONOR, I THINK AS I SAID EARLIER, WHAT I HOPE TO DO HERE IS GIVE YOU A GLOSSARY OF THE BACKGROUND SCIENCE, BECAUSE AS YOU READ THE '499 AND THE '712 PATENT, THE PATENTS DO SPEND A FAIR AMOUNT OF TIME DESCRIBING THIS DISEASE AND DESCRIBING THESE PARTICULAR MOLECULES AND HOW THEY WORK TO TREAT THE DISEASE.

A LOT OF THE TERMINOLOGY I'M GOING TO USE HERE AND TRY TO, THE GLOSSARY I'M GOING TO TRY TO PROVIDE YOU, I THINK YOU ARE GOING TO BE HEARING THESE TERMS IN THE HEARING NEXT WEEK, AND I THINK IT WILL MAKE THINGS MORE UNDERSTANDABLE.

THE COURT: OKAY. GOOD.

MR. MCCANN: I WASN'T PLANNING TO DO MUCH DISCUSSION OF THE CLAIM TERMS, I WAS GOING TO SAVE THAT FOR THE MARKMAN HEARING. THE PROFESSOR DID JUST GO THROUGH SOME ASPECTS OF THAT.

I JUST WANT TO LEAVE, WHEN I'M DONE, I JUST WANT TO LEAVE A COUPLE OF POINTS OF OUR VIEW OF SOME OF THE COURT'S QUESTIONS. AGAIN, PRIMARILY THAT WOULD BE FOR THE MARKMAN ARGUMENT.

AND I DO FEEL YOUR HONOR, WITH YOUR PERMISSION, FOR THE SAKE OF THE RECORD I WANT TO OBSERVE SINCE THE COURT OF APPEALS WILL SOME DAY BE LOOKING AT ALL OF THIS, THAT THE PROFESSOR'S COMMENTARY TODAY WAS OF COURSE NOT UNDER OATH AND MERCK IS NOT OFFERING HIS INFORMATION AS EXTRINSIC EVIDENCE ANY MORE THAN I'M OFFERING MINE, FOR PURPOSES OF CLAIMS CONSTRUCTION.

THE COURT: WELL, FRANKLY, I EVEN QUESTION WHETHER I SHOULD HAVE THIS REPORTED, AND IT SEEMS TO BE THE PRACTICE TO REPORT THE TUTORIAL, BUT I DON'T CONSIDER THIS EVIDENCE. I SUPPOSE ONE COULD IMPEACH BASED ON IT, BUT I LEAVE THAT TO YOU.

MR. MCCANN: THAT WOULD BE MY PLAN TO IMPEACH BASED ON IT, YOUR HONOR, BUT I DIDN'T WANT THE COURTS OF APPEALS LATER ON TO THINK AH HA, THERE WAS AN EXPERT TESTIFYING --

THE COURT: OF COURSE. I DIDN'T CONSIDER IT AS TESTIMONY MYSELF, I DON'T THINK IT WAS OFFERED AS SUCH, WAS IT?

DR. WUEST: IT WAS NOT IN THIS CASE, YOUR HONOR.

THE COURT: THANK YOU. THEN OUR RECORD IS CLEAR.

MR. MCCANN: THANK YOU, YOUR HONOR.

SO THE '499 PATENT IS THE ONE THAT I WILL GO THROUGH WHAT THEY ARE AND WHAT THE SPECIFICATIONS ARE. AND THEY DO CONCERN THE NUCLEOSIDE DERIVATIVES OF INHIBITORS OF RNA-DEPENDENT RNA VIRAL POLYMERASE.

AND THE PATENT GOES ON TO DESCRIBE HOW --

THE COURT: AND YOU NEED TO SPEAK SLOWLY BECAUSE MY COURT REPORTER -- THESE ARE NOT WORDS KNOWN TO NORMAL PEOPLE.

MR. MCCANN: TRUE.

THE PATENT DOES GO ON TO DESCRIBE HOW IF YOU INHIBIT SOMETHING CALLED THE NS5B POLYMERASE, YOU CAN SUCCESSFULLY TREAT THIS DISEASE.

SO WHAT I'M GOING TO DO IS GIVE YOU A LITTLE BACKGROUND ON THE DISEASE, A LITTLE BACKGROUND ON HOW THE DISEASE USED TO BE TREATED, HOW IT IS TREATED TODAY, AND THEN HOW THIS DRUG SOFOSBUVIR ACTUALLY WORKS TO DEFEAT THE VIRUS.

SO FIRST, A LITTLE BIT ABOUT VIRUSES IN GENERAL. THEY ARE SELF REPLICATING ORGANISMS.

WHAT YOU SEE DEPICTED HERE ON SLIDE 4 IS SOMETHING CALLED A VIRION, THAT'S A VIRUS PARTICLE. AND IT IS A SELF-CONTAINED GENOME. IN OTHER WORDS, THAT PARTICLE, AND THERE ARE MILLIONS OF THEM IN YOUR BODY IF YOU WERE INFECTED WITH THIS DISEASE, AND EVERYTHING THAT THE VIRUS NEEDS TO CREATE MORE PARTICLES.

VIRUSES CAN BE BASED ON AN RNA OR A DNA GENOME. IT IS THE CASE WITH HEPATITIS C THAT IT IS AN RNA BASED GENOME.

HEPATITIS C IS A MEMBER OF A FAMILY OF VIRUSES. THERE ARE SIX MAJOR GENOTYPES, AND THAT'S A TERM YOU WILL BE HEARING THROUGHOUT THIS CASE.

A GENOTYPE IS A VARIATION OF THE GENOME WHICH EXPLAINS WHY IT'S -- YOUR CLERK AND I ARE BOTH HUMAN BEINGS, BUT HER HAIR IS LIGHTER THAN MINE, MY EYES ARE BROWN, THE GENOTYPE IS WHAT GIVES YOU THOSE VARIATIONS BETWEEN THE PERSON SHARING THE SAME GENOME.

THE RELEVANCE OF THAT FOR TREATING HEPATITIS C IS THAT SOME DRUGS WORK WELL AGAINST ONE GENOME ON ONE GENOTYPE, BUT NOT ANOTHER. SO YOU MIGHT WORK A LONG TIME DEVELOPING A DRUG THAT CAN DO A GREAT JOB AGAINST GENOTYPE 1. THERE'S FIVE OTHER MAJOR SUBTYPES THAT YOU HAVE TO BE ABLE TO DEAL WITH AS WELL. SO IT'S VERY COMPLICATED.

HEPATITIS C IS BLOOD BORNE, CONTAGION. AN IMPORTANT POINT HERE IS THAT IT IS ASYMPTOMATIC WHEN YOU FIRST CONTRACT IT, SO YOU DON'T KNOW YOU HAVE IT. AND YOU WON'T KNOW, IN FACT FOR YEARS, UNLESS YOU ARE TESTED. ONLY WHEN THE LIVER IS BEGINNING TO SCAR AND DEVELOP THE CONDITION CIRRHOSIS, AND THEN YOU REALIZE YOU ALREADY HAVE SUFFERED SUBSTANTIAL DAMAGE.

I THINK I CAN JUST TO KEEP THINGS MOVING, I WILL SKIP SOME OF THIS.

IT'S A BIG PROBLEM. THERE'S 2 PERCENT OF THE WORLD'S POPULATION HAS THE DISEASE. HERE IN THE UNITED STATES, THERE ARE 3.2 MILLION PEOPLE WHO ARE INFECTED.

NOW BECAUSE THE DISEASE IS A SILENT KILLER, ONLY ABOUT 50 PERCENT OF THE PEOPLE WHO HAVE IT EVEN KNOW THAT THEY HAVE IT. IF YOU DON'T GET THE DISEASE TREATED, YOUR LIVER TISSUE DOES SCAR AND YOU DO THEN SUFFER THIS CONDITION CALLED CIRRHOSIS.

THE ONLY REMEDY FOR THAT, IF IT'S AT AN ADVANCED ENOUGH STAGE, IS TO HAVE A LIVER TRANSPLANT. SO HEPATITIS C IS THE PRIMARY INDICATOR FOR LIVER TRANSPLANTS HERE IN THE UNITED STATES. AS YOU CAN SEE, IT'S ALMOST DOUBLE WHAT YOU SEE FOR ALCOHOLIC CIRRHOSIS.

OKAY. SO NOW JUST A LITTLE BIT ABOUT HOW THE DISEASE WAS TREATED AND THAT'S PART OF THE BACKGROUND OF THE PATENT YOUR HONOR YOU WERE REVIEWING SPECIFICATIONS, PERHAPS YOU SAW.

THE COURT: I DID.

MR. MCCANN: SO BEFORE 2011 HEPATITIS C WAS FIRST IDENTIFIED IN 1989. PEOPLE KNEW IT WAS OUT THERE BEFORE THEN BUT IT WAS FIRST CHARACTERIZED IN 1989.

AND THE TREATMENT THAT WAS DEVELOPED AND WHICH WAS THE STANDARD TREATMENT ALL THE WAY THROUGH 2011 WAS A WEEKLY INJECTION OF SOMETHING CALLED INTERFERON AND THEN MULTIPLE PILLS OF A DRUG CALLED RIBAVIRIN.

AND INTERFERON WOULD BOOST YOUR BODY'S OWN IMMUNE SYSTEM TO TRY TO HELP YOUR BODY DEFEAT THE DISEASE. AND THEN RIBAVIRIN WOULD SOMEHOW INHIBIT THE VIRAL SYNTHESIS.

NOBODY REALLY KNOWS EXACTLY HOW RIBAVIRIN WORKED, BUT I'M

PROBABLY OVERSTATING IT TO SAY THAT IT WORKED, BECAUSE USING THAT STANDARD OF CARE OF INTERFERON AND RIBAVIRIN, ONLY ABOUT 50 PERCENT OF THE PEOPLE WOULD ACTUALLY BE CURED.

ONE OF THE BIGGEST PROBLEMS WITH THIS WAS HOW SICK THE TREATMENT MADE YOU. SO IF YOU WERE SUFFERING FROM HEPATITIS, YOU WOULD TAKE THIS TREATMENT FOR A YEAR. EVERY WEEK YOU WOULD HAVE TO GO GET AN INTERFERON INJECTION. AND IF YOU TOOK IT ON A FRIDAY, LET'S SAY, YOU WOULD FEEL LIKE YOU HAD THE FLU THROUGH SATURDAY, SUNDAY, MONDAY AND EVEN TUESDAY, UNABLE TO WORK.

BY WEDNESDAY OR THURSDAY YOU WOULD BE BACK UP ON YOUR FEET, BUT NOW FRIDAY IS ROLLING AROUND AGAIN AND YOU HAVE TO TAKE THE INJECTION EVERY WEEK, WEEK IN AND WEEK OUT, FOR A YEAR.

AND THE RESULT OF THAT IS HIGH DISCONTINUATION. PEOPLE WOULD RATHER HAVE THE DISEASE, BECAUSE YOU DON'T REALLY FEEL BAD, THAN THEY WOULD WANT TO TAKE THE TREATMENT.

IN 2011 THERE WERE SOME FURTHER IMPROVEMENTS, I WILL MOVE PAST THIS RATHER QUICKLY, SOMETHING CALLED A PROTEASE INHIBITOR WAS ADDED TO THE TREATMENT.

YOU ARE LOOKING AT SLIDE 16 YOU CAN SEE IN ADDITION TO INTERFERON AND RIBAVIRIN WHICH YOU STILL HAVE TO TAKE, AND YOU HAD TO TAKE FOR SIX MONTHS AND NOT A YEAR, THAT WAS THE ADVANTAGE OF THESE ADDITIONAL DRUGS, BUT YOU WOULD HAVE TO TAKE MORE PILLS.

SO 12 PILLS OF BOCEPREVIR, IF THAT WAS YOUR TREATMENT, PLUS THE 5 RIBAVIRIN, PLUS THE WEEKLY SHOT.

SO AGAIN, DISCONTINUATION RATES ARE HIGH. PEOPLE ARE REALLY NOT BEING TREATED. AND THAT'S THE RESULT. OF THAT 3.2 MILLION, ONLY 15 PERCENT WOULD ACTUALLY SEE THIS THROUGH TILL THE END.

OKAY. NOW IN 2013, THE DRUG THAT'S AT ISSUE IN THIS CASE, SOFOSBUVIR, WAS LAUNCHED HERE IN THE UNITED STATES.

AND I'M JUST GOING TO BRIEFLY TALK ABOUT SOFOSBUVIR AND HOW IT TREATS THE DISEASE, FIRST AT A HIGH LEVEL IN TERMS OF WHAT THE PATIENTS DO, AND THEN I'M GOING TO FOCUS MORE ON THE STRUCTURE OF THE MOLECULE AND GIVE THE COURT SOME TERMS TO UNDERSTAND HOW, WHAT YOU CALL THE DIFFERENT PORTIONS OF THIS MOLECULE, AND THEN A LITTLE BIT ABOUT HOW IT WORKS.

SO IT WAS APPROVED IN 2013, IT HAS FEWER ADVERSE SYMPTOMS, THE ACTIVE INGREDIENT SOFOSBUVIR, THE ORIGINAL DRUG SOVALDI YOU STILL TOOK WITH RIBAVIRIN OR INTERFERON, THAT WAS IN DECEMBER 2013.

BUT WITHIN A YEAR, GILEAD LAUNCHED A NEW GENERATION, HARVONI. THAT'S NOW A SINGLE PILL. THE SHOT IS GONE, THE RIBAVIRIN IS GONE, FOR GENOTYPE 1. YOU ONLY TAKE THE DRUG FOR 8 TO 24 WEEKS, SO A MUCH SHORTER COURSE OF THERAPY. AND YOUR SIDE EFFECTS, IF YOU HAVE THEM, ARE FATIGUE AND A HEADACHE. THE TERRIBLE CONSEQUENCES OF INTERFERON ARE NOW REMOVED ENTIRELY.

GILEAD IS CURRENTLY DEVELOPING A REPLACEMENT FOR HARVONI. SO YOU HAVE -- HARVONI IS SOFOSBUVIR PLUS A DRUG CALLED LEDIPASVIR. YOU ARE GOING TO TAKE LEDIPASVIR OUT AND PUT A NEW DRUG IN AND THAT DRUG WILL BE A SINGLE TABLET WITH THE SAME SIDE EFFECTS, SAME COURSE OF THERAPY, BUT GOOD AGAINST ALL SIX GENOTYPES.

OKAY. SO THAT'S THE BACKGROUND OF THE DISEASE, YOUR HONOR, AND HOW IT'S TREATED. NOW INTO THE CHEMISTRY.

THE COURT: THE EASY PART IS OVER.

MR. MCCANN: IT IS.

AND I'M SURE PROFESSOR WUEST WILL CORRECT ME, I LIKE TO JOKE AND MR. FARRELL LIKES TO TEASE ME THAT I'M ABOUT THREE DEGREES SHORT OF A PHD HERE, BUT I WILL DO MY BEST TO EXPLAIN THESE --

THE COURT: AND SIX DEGREES OF SEPARATION.

MR. MCCANN: YES.

SO FIRST, THERE ARE TWO TERMS THAT YOU SEE IN THE PATENT AND THAT YOU WILL HEAR AT THE MARKMAN HEARING AND THROUGHOUT THIS CASE, THEY ARE NUCLEOSIDE AND NUCLEOTIDE.

SO I'M GOING TO START WITH NUCLEOSIDE AND GO THROUGH THAT AND THEN I WILL EXPLAIN TO YOUR HONOR WHAT THE DIFFERENCE IS BETWEEN THAT AND THEN THE NUCLEOTIDE.

SO WHAT YOU ARE SEEING HERE IS A NUCLEOSIDE. AND THE MOLECULE HAS REALLY THREE PARTS I WANT TO FOCUS ON.

FIRST IS WHAT'S CALLED THE NUCLEOBASE, THE SECOND IS THE

SUGAR RING, AND THE THIRD IS, WHICH I WILL SPEND A LITTLE BIT MORE TIME ON LATER, THE PART OF THE SUGAR RING WHICH I WILL REFER TO AS THE 5 PRIME POSITION.

SO IF YOUR HONOR LOOKS AT THE SUGAR RING, WHICH IS THAT PART IN THE CENTER, YOU SEE HOW THERE'S THE RED CIRCLES, AND PROFESSOR WUEST EXPLAINED TO YOU THAT WHEN YOU SEE AN ANGLE WITHOUT A LETTER THERE, THAT INDICATES THERE'S A CARBON ATOM PRESENT. AND PEOPLE DESCRIBE THE POSITIONS ON THE SUGAR RING OF THESE MOLECULES, AS I'VE INDICATED HERE.

SO THE VERY FIRST ONE YOU SEE IS CALLED 1 PRIME, THEN MOVING DOWN TO THE LEFT, THIS IS ON SLIDE 23, IS 2 PRIME, THEN 3 PRIME, 4 PRIME, AND THEN COMING UP OFF THE RING IS THE 5 PRIME POSITION.

THERE'S GOING TO BE A LOT OF DISCUSSION NEXT WEEK ABOUT THAT 5 PRIME POSITION, A LOT OF DISCUSSION IN THIS CASE OVERALL ABOUT THAT 2 PRIME POSITION. AND I WILL GIVE YOU A LITTLE BIT OF A PREVIEW OF THAT TODAY.

NOW I SAID THAT ONE OF THE POSITIONS ON THE MOLECULE IS CALLED THE NUCLEOBASE, THERE ARE ACTUALLY FOUR, AND RNA, THEY ARE ADENINE, GUANINE, URACIL AND CYTOSINE.

AND YOUR HONOR MIGHT REMEMBER DNA HAS ADENINE, GUANINE, CYTOSINE AND THYMINE, SO THE DIFFERENCE BETWEEN AN RNA AND DNA MOLECULE, ONE DIFFERENCE IS THEY SHARE THREE BASIS THAT ARE THE SAME, BUT THE FOURTH IS DIFFERENT.

AND IN YOUR BODY WHEN THESE MOLECULES ARE DOING THEIR

JOB, THEY SORT OF PAIR UP IN A PATTERN. SO THE A, THE MOLECULES THAT HAVE THE ADENINE BASE, ALWAYS PEAR UP WITH A MOLECULE THAT HAS A URACIL BASE. AND THEN GUANINE WITH CYTOSINE.

AND ONE MORE BIT OF INFORMATION ABOUT THE NUCLEOBASE, THEY ARE BROKEN INTO TWO CATEGORIES. YOU SAW THAT -- ACTUALLY, IF YOU JUST SEE THE PATTERN, I SAID THAT ADENINE ALWAYS PAIRS WITH URACIL, SO YOU ALWAYS HAVE A DOUBLE RING THAT PAIRS WITH A SINGLE RING, AND GUANINE ALWAYS PAIRS WITH CYTOSINE.

IF YOU LOOK AT THE NEXT SLIDE, JUST FOR THE NOMENCLATURE IN THE PATENT, THE DOUBLE RINGS HAVE A SHORTER NAME, THEY ARE CALLED PURINES. THE SINGLE RINGS ARE CALLED PYRIMIDINES.

THE COURT: I'M NOT SURE WHAT YOU MEAN BY DOUBLE RINGS.

MR. MCCANN: IF YOU LOOK AT THE PURINE, YOUR HONOR, THERE IS TWO RINGS, EACH WITH TWO NITROGENS. SO YOU SEE THE FIRST RING HERE, I SHOULDN'T HAVE USED BLUE ON BLUE, AND THAT'S RING NUMBER 1 AND THAT'S FUSED HERE TO RING NUMBER 2.

THE COURT: OH, OKAY.

MR. MCCANN: AND THEN FOR THE PYRIMIDINE, THERE'S ONLY A SINGLE RING.

ALL RIGHT, NOW I SAID THAT WAS THE NUCLEOSIDE, NOW THERE'S ALSO A CONCEPT HERE CALLED THE NUCLEOTIDE. AND THE BIG DIFFERENCE IS THE NUCLEOSIDE HAS AN OH AT THE 5 PRIME POSITION, AND THEN THE NUCLEOTIDE HAS PHOSPHOROUS ATOMS.

SO I'M GOING TO JUMP AHEAD A LITTLE BIT TO EXPLAIN THE RELEVANCE OF THAT AND THEN I'M GOING TO TOUCH ON IT AGAIN LATER IN THE PRESENTATION.

SO YOUR BODY HAS NUCLEOSIDES NATURALLY OCCURRING, AND WHEN IT'S TIME FOR THESE NUCLEOSIDES TO BE INCORPORATED INTO A GROWING STRAND OF RNA OR DNA AS THE CASE MIGHT BE, THE OH IS REPLACED WITH THESE PHOSPHOROUS ATOMS.

FIRST IT BECOMES 1 PHOSPHOROUS, THE OH COMES OFF, AND THEN A FIRST PHOSPHOROUS ATOM IS ADDED, AND A SECOND, AND THEN A THIRD AND THE PROCESS IS CALLED PHOSPHORYLATION. AND THAT'S REQUIRED FOR THE MOLECULES TO BE ABLE TO BE LINKED INTO THE GROWING RNA CHAIN. SO THEY CAN'T DO IT WHEN THEY HAVE AN OH THERE, YOUR BODY HAS TO ADD THE THREE P'S.

AND JUST TO KEEP THINGS STRAIGHT, FOR THE SCIENTISTS THEY CALL THAT A NUCLEOTIDE WHEN THE P'S ARE PRESENT.

AND YOU CAN SEE, YOUR HONOR, THAT IF YOU ONLY HAVE ONE, YOU CALL IT A MONOPHOSPHATE. IF YOU HAVE TWO, YOU CALL IT A DIPHOSPHATE, AND IF YOU HAVE THREE, YOU HAVE A TRIPHOSPHATE.

I JUST REFERRED TO THIS A SECOND AGO, BUT HERE ON SLIDE 27 WHICH YOU CAN SEE IS, IN YOUR BODY, THIS IS A NATURAL PROCESS YOUR BODY WILL GO THROUGH, AND THIS IS SEPARATE AND APART FROM ADMINISTERING A DRUG, THIS IS JUST HAPPENING INSIDE YOURSELVES ALL THE TIME.

YOU HAVE YOUR NUCLEOSIDE WITH A GIVEN BASE, LET'S SAY ADENINE, THE ONE WE LOOKED AT BEFORE. AND THE OH IS REPLACED

WITH AN ENZYME CALLED KINASE WITH THE FIRST PHOSPHOROUS ATOM, THEN THE SECOND AND THE THIRD AND SO ON. SO THAT'S WHAT'S NECESSARY FOR THESE CHAINS TO BE BUILT.

OKAY. NOW YOUR HONOR, I'M MINDFUL OF YOUR TIME, I KNOW YOU HAVE A JURY DELIBERATING.

THE COURT: THEY ARE QUIET FOR NOW, SO KEEP GOING.

MR. MCCANN: I DO HAVE THESE TWO SHORT VIDEOS, SO I'M GOING TO JUST PLAY THEM.

THE COURT: SO, GO AHEAD. WE ARE DOING FINE.

(WHEREUPON, A VIDEO WAS PLAYED IN OPEN COURT.)

MR. MCCANN: SO WHAT HAPPENS, YOUR HONOR, IS THE VIRUS PARTICLE, THAT LITTLE VIRION WE SAW IN THE BEGINNING, PENETRATES INTO YOUR CELL, AND IT'S LIKE A HARD PROTEIN OUTER SHELL THAT BREAKS APART. OUT COMES THE RNA.

THE RNA IS THEN PROCESSED BY THAT LITTLE STRUCTURE THAT'S POKING OUT, THAT LITTLE BROWN THING I GUESS, THAT IS CALLED THE RIBOSOME, AND THAT'S A LITTLE ENGINE FOR MAKING NEW RNA.

AND WHAT IT DOES FIRST IS IT GENERATES WHAT THIS LONG, COLORED POLYPROTEIN HERE AT THE BOTTOM, THERE'S TEN OF THEM IN THERE, ONE OF THEM IS THIS NS5B POLYMERASE.

SO IT'S GOING TO BE INHIBITING THAT NS5B POLYMERASE FROM DOING IT'S JOB, THAT'S THE KEY TO HOW THE DRUGS, THE TECHNOLOGY IN THIS CASE WORK.

IF WE COULD PROCESS, MS. SANCHEZ.

(WHEREUPON, A VIDEO WAS PLAYED IN OPEN COURT.)

MR. MCCANN: SO I WILL SKIP THIS ONE AND USE THIS SLIDE TO EXPLAIN WHAT'S HAPPENING.

SO YOU SAW THE VIRUS PARTICLE OPENS UP, THE RNA COMES OUT AND THEN THE NS5B POLYMERASE BEGINS TO ASSEMBLE A NEW RNA STRAND.

SO WHAT YOU HAVE IS ONE HALF AND THEN THE ENZYME, KIND OF WORKING LIKE A ZIPPER, COMES ALONG PAIRING UP THE PARTICULAR BASE PAIR.

SO IF YOU HAVE THIS ORANGE, YELLOW, FOR EXAMPLE IF THAT BOTTOM ONE IS A, THE TOP ONE, THE YELLOW IS U. AND THEN THE RED IS C, THEN THE TOP IS G, AND SO ON.

SO WHAT THE NS5B POLYMERASE IS DOING IS IT'S GOING ALONG THE CHAIN. AND IT SEES AH, THE NEXT MOLECULE I SEE IS ADENINE BASE, I'M GOING TO TAKE A URACIL AND PAIR THAT UP.

SO WHAT YOU WANT TO DO IS YOU WANT TO INSERT A MOLECULE THAT'S DEFECTIVE THAT THE ENZYME WILL THINK IS THE NATURALLY OCCURRING, IN THE CASE OF SOFOSBUVIR, THE NATURALLY OCCURRING URACIL BASED NUCLEOTIDE.

YOU WANT TO TRICK IT INTO THINKING THAT'S WHAT IT SHOULD PUT ON AND IT DOES, BUT WHEN IT DOES BECAUSE IT HAS BEEN ALTERED, IT NO LONGER, THE NS5B CAN NO LONGER DO IT'S JOB, IT CAN'T ATTACH TO THE NEXT MOLECULE IN THE CHAIN AND THE CHAIN TERMINATES AND THEN THE VIRUS CAN'T REPLICATE, AND WHEN THE VIRUS CAN'T REPLICATE THEN EVENTUALLY YOUR BODY WILL KILL IT OFF.

OKAY. SO LOOKING A LITTLE BIT ABOUT SOFOSBUVIR, AND WE WON'T SPEND A WHOLE LOT OF TIME ON THIS.

SOFOSBUVIR, THE DEVELOPMENT BEGAN AT A COMPANY CALLED PHARMASSET BEGINNING IN 2003. AND PHARMASSET DISCOVERED FIRST HOW TO BREAK THE ZIPPER, RIGHT.

AND THAT WAS THIS -- SO IN THE NATURALLY OCCURRING MOLECULE WHICH YOU SEE ON THE LEFT, THERE'S AN OH AT THAT 2 PRIME POSITION. THE SCIENTISTS AT PHARMASSET LEARNED THAT IF YOU REPLACE THAT WITH A FLOURINE ATOM, POINT IT DOWN, AND THAT'S WHAT'S CALLED A METHYL GROUP, POINT IT UP, THAT'S GOING TO BE IMPORTANT FOR THE NS5B POLYMERASE TO THINK, AH HA, THIS IS A NATURALLY OCCURRING MOLECULE.

BUT IT'S DEFECTIVE BECAUSE YOU CHANGE WHAT HAPPENS IN NATURE. YOU PUT SOMETHING ELSE THERE AND THAT WAS GOING TO BREAK THAT PROCESS.

SO THAT WAS THE FIRST DISCOVERY, IT'S A GENERATION AWAY, BUT EVENTUALLY SOFOSBUVIR EMPLOYS THAT PART OF THE TECHNOLOGY.

BUT IT'S NOT ENOUGH TO KNOW HOW TO BREAK THE ZIPPER, YOU HAVE TO GET THIS BROKEN PIECE TO THE RIGHT SPOT IN YOUR LIVER CELL WHICH MEANS YOU HAVE TO GIVE A DRUG TO A PATIENT WHO SWALLOWS IT AND THAT'S GOING TO BE DISSOLVED INTO THEIR STOMACH, GET INTO THEIR BLOOD STREAM AND EVENTUALLY MAKE ITS WAY TO THE LIVER.

THE COURT: THEY FIGURED OUT WHAT THE GOAL WAS, THEY JUST DIDN'T HAVE THE PLAN TO GET THERE.

MR. MCCANN: EXACTLY. AND THIS IS NOT AN EASY THING.

I'M NOT GOING TO SPEND A LOT OF TIME ON PRODRUGS, YOU JUST HEARD A LOT ABOUT THEM, BUT IT'S THE BASIC IDEA AS PROFESSOR WUEST SAID, IS YOU DESIGN A MOLECULE THAT IS GOING TO DELIVER THE RIGHT THING AT THE RIGHT PLACE AT THE RIGHT TIME. AND THERE ARE MANY, MANY DIFFERENT WAYS TO DO THAT, AS YOU WILL HEAR SOMETHING ABOUT NEXT WEEK, BUT BASICALLY I WILL SHOW YOU HOW SOFOSBUVIR WORKS.

AND I HAVE, THE PROFESSOR CARVED OUT SOME OF THESE THINGS, WHY YOU HAVE PRODRUGS AND THAT SORT OF THING.

SO THIS PATENT IS, I THINK THE KEY DATE IS AROUND 2002 WE WERE DISCUSSING EARLIER AT THE BEGINNING OF THE HEARING. AND AT THAT TIME PEOPLE CERTAINLY KNEW THAT THERE WERE DIFFERENT WAYS YOU COULD DELIVER A NUCLEOSIDE TO SOMEBODY TO GET INTO THEIR BODY AND TRY TO DO THIS JOB.

MANY PEOPLE THOUGHT THE WAY TO GO WAS TO DELIVER A DRUG WITH JUST OH IN THE 5 PRIME POSITION THE SAME WAY THAT OCCURS IN NATURE. THAT CERTAINLY CAN WORK, THAT'S ONE WAY MANY COMPANIES PURSUED, AND IT'S ACTUALLY -- MANY OF THE COMPOUNDS YOU SEE IN THIS PATENT EMPLOY THAT TECHNOLOGY.

BUT YOU COULD ALSO TRY TO MAKE A PRODRUG, SO LEAVING IT THE WAY IT IS NORMALLY IN NATURE, THAT'S NOT A PRODRUG, BUT YOU COULD DO THINGS TO IMPROVE YOUR ABILITY TO GET THIS DRUG WHERE YOU WANT IT.

WHAT YOU ARE SEEING IS THE SCREEN HERE AT SLIDE 36 IS AN

ARTICLE BY A MAN NAMED WAGNER, IT'S CITED IN THE PATENT. AND YOU CAN SEE THAT THESE ARE ALL PRODRUG STRATEGIES THAT ONE COULD USE TO DELIVER NUCLEOSIDE THAT WAGNER GOES THROUGH. NONE OF THEM ARE THE EXACT METHOD THAT SOFOSBUVIR USES.

AND EACH OF THEM, THESE ARE SORT OF HEADINGS ON WAYS TO DO SOMETHING, WITHIN EACH HEADING IN THE ARTICLE IS A DESCRIPTION OF, YOU KNOW, MORE SUBWAYS, I GUESS, SO LOTS OF DIFFERENT WAYS TO DO THIS.

SO HOW DOES SOFOSBUVIR WORK? OR HOW DID THEY SOLVE THE PROBLEM WITH SOFOSBUVIR?

FIRST, THEY WENT WITH THE NATURAL URACIL BASE. THIS IS WHAT OCCURS IN NATURE. THEY USE THAT MODIFIED SUGAR, WHICH I DESCRIBED BEFORE, WHERE INSTEAD OF OH AT 2 PRIME THEY PUT A FLOURINE AND A METHYL, THAT'S THE BROKEN ZIPPER. THEN THEY MADE A PRODRUG MOIETY.

AND WHAT THEY DID WAS THEY DECIDED INSTEAD OF HAVING THE OH THERE, WE WANT TO HAVE THE FIRST STEP OF THAT PHOSPHORYLATION, THAT FIRST PHOSPHOROUS ALREADY ON THE MOLECULE. BECAUSE WHAT WE FOUND WAS AS WE DELIVER THIS DRUG TO THE BODY, IF YOU USE WHAT OCCURS NATURALLY, THE OH MAYBE WOULD GET INTO THE LIVER CELL, BUT FOR SOME REASON THAT PHOSPHORYLATION WHAT WOULD NATURALLY HAPPENS IN YOUR BODY WHERE OH IS REPLACED BY 1P, AND THEN 2P, AND 3P'S, IT WAS BREAKING DOWN.

SO THEY FIGURED OUT -- AND YOU WILL NOTICE THIS WAS 2007,

THIS IS FOUR YEARS LATER IT TOOK TO FIGURE THIS OUT. THEY THOUGHT WELL, HOW ABOUT IF WE SKIP THE FIRST STEP, IF WE START WITH THE MOLECULE THAT ALREADY HAS THE FIRST P ON THERE, MAYBE THAT WILL WORK BETTER, AND IN FACT IT DOES.

SO WHEN THIS MOLECULE IS DELIVERED INTO YOUR LIVER CELL, THE FIRST P IS ALREADY ON, YOU DON'T HAVE TO DO THE FIRST STEP. AND THEN IT GOES TO THE SECOND, THE THIRD, GETS INCORPORATED BY THAT NS5B INTO THE CHAIN AND BREAKS THE CHAIN. OKAY.

SO SOFOSBUVIR CROSSES THE LIVER CELL, IT BEGINS AS THE MONOPHOSPHATE AND EVENTUALLY WILL METABOLIZE TO THE TRIPHOSPHATE.

AND I JUST WANT TO TALK BRIEFLY ABOUT HOW THAT WORKS. AND AGAIN, JUST BACKGROUND YOUR HONOR TO SHOW YOU THIS IS NOT LEGOS, IT'S NOT TAKING A REALLY EASILY KNOWN SOLUTION AND PUTTING IT ON HERE.

SO SOFOSBUVIR IS A PRODRUG OF THE MONOPHOSPHATE, MEANING I BEGIN WITH P ALREADY ON THERE. I HAVE THIS WHOLE STRUCTURE CALLED THE PHOSPHOROUS ENTITY. WHEN I INGEST THIS MOLECULE, AN ENZYME CALLED A CARBOXYLASE STRIPS OFF THIS PORTION HERE, THIS IS CALLED AN ESTER, IT STRIPS THAT OFF LEAVING INSTEAD OF THE STRUCTURE YOU SAW THERE, AND IN THE RED CIRCLE YOU SEE THE OH.

AND THEN THIS RED CIRCLED AREA AND THAT BLUE RECTANGLE AREA, THEY HAVE A PROPENSITY TO REACT WITH EACH OTHER. AND SO AS SOON AS THESE TWO ARE EXPOSED TO EACH OTHER, THERE'S A RAPID STEP WHERE THE FENNEL GROUP, THAT'S THIS RING YOU SEE HERE, THE

FENNEL GROUP IS STRIPPED OFF, THAT LEAVES YOU WITH THE STRUCTURE THAT YOU SEE ON THE RIGHT AT STEP NUMBER THREE WHERE YOU HAVE THE GREEN CIRCLE.

AND THEN THE LAST STEP IS THERE'S SOMETHING CALLED AN ENZYME CALLED A PHOSPHORAMIDASE THAT TARGETS THIS NITROGEN BEARING GROUP AND STRIPS THAT OFF. AND THE END RESULT IS THE FIRST P PRESENT, AND THEN YOUR BODY WILL ADD NUMBER TWO AND NUMBER THREE.

OKAY. SO WE ALREADY DISCUSSED THIS WITH PROFESSOR WUEST'S PRESENTATION, BUT IN SUMMARY YOU INGEST SOFOSBUVIR, IT PENETRATES THE LIVER CELL, AS YOU SEE ON THE LEFT AS SOFOSBUVIR, THE CHEMICAL STEPS I JUST DESCRIBED OCCUR.

YOU ARE LEFT WITH THAT MONOPHOSPHATE, THEN YOUR BODY TAKES IT FROM THERE AND ADDS THE SECOND PHOSPHOROUS AND THE THIRD.

OKAY. AND PROFESSOR WUEST STOLE MY THUNDER AND PLAYED BY VIDEO, SO I WILL SKIP THAT, BUT YOUR HONOR HAS IT.

OKAY. SO THE LAST THING I WANTED TO COVER AND THEN I JUST WANT TO TALK BRIEFLY ABOUT COMPOUNDS OF THE INVENTION AND THAT SORT OF THING, IS JUST HOW TO READ ONE OF THESE CLAIMS. I DON'T KNOW IF YOUR HONOR HAS HAD CHEMISTRY CASES BEFORE.

THE COURT: NO, I HAVEN'T.

MR. MCCANN: SO CLAIM 1 OF THE '499 PATENT IS SOMETHING CALLED THE MARKUSH STRUCTURE.

SO WHAT THE INVENTOR WILL DO IS THEY WILL SAY WELL, IT

WOULD OF COURSE BE VERY DIFFERENT FOR ME TO LIST OFF ONE BY ONE EVERY CHEMICAL STRUCTURE THAT I'M CLAIMING IN MY INVENTION, AND THIS PATENT PROBABLY COVERS THOUSANDS OF POSSIBILITIES. AS YOUR HONOR KNOWS, I THINK SOMETHING LIKE 154 EXAMPLES THAT ARE DRAWN OUT IN THE SPECIFICATIONS AND THEN THE CLAIMS WHICH ARE DIFFERENT HAVE THOUSANDS OF POSSIBILITIES. AND SO THE WAY YOU DO THAT IS YOU USE VARIABLES.

AND SO YOU INDICATE, YOU RECALL I WAS TALKING ABOUT THAT 5 PRIME POSITION, FOR EXAMPLE, ON THE SUGAR RING. WELL THAT'S Y, Y IS THE 5 PRIME POSITION. AND Y SAYS I CAN ADD ALL KINDS OF THINGS, I CAN ADD MY HYDROGEN AND MY C1 TO 10 ALKYLCARBONYL OR MY DIFFERENT STRUCTURES USING PHOSPHOR ATOMS. (SIC)

AND SO WHEN YOU ARE READING ONE OF THESE CLAIMS, WHAT YOU DO IS YOU SAY OKAY, LET'S SAY I WANT TO CONSTRUCT A PARTICULAR MOLECULE, MERCK HAD A LEAD COMPOUND CALLED 608 AND IT IS ONE OF THE EXAMPLES IN THE PATENT, YOU CAN GO THROUGH AND SORT OF MARRY UP IN A GIVEN STRUCTURE HOW THAT COMPOUND LINES UP WITH THESE VARIABLES.

SO THAT, YOUR HONOR, IS THE BASIC PRESENTATION I WANTED TO GIVE. I DO WANT TO TALK ABOUT A LITTLE BIT ABOUT THE PRODRUG OF THE COMPOUND OF THE INVENTION.

YOU WERE ASKING SOME QUESTIONS BEFORE AND I THINK THEY WERE SORT OF DIRECTED AT, IS THE ACTIVE METABOLITE, IS THAT THE COMPOUND OF THE INVENTION AS THE THING YOU GIVE, WHAT THE PATENT YOU ARE REFERRING TO IS, THE PRODRUG OF THE COMPOUND OF

THE INVENTION. AND THIS IS NOT THE MARKMAN ARGUMENT, AND I WILL CERTAINLY --

THE COURT: I OPENED THE DOOR.

MR. MCCANN: WELL, I WILL CERTAINLY GO INTO IT IN MORE DETAIL NEXT WEEK. BUT NO, IT IS NOT.

THE CLAIM, THIS CLAIM OF THIS PATENT HAS BOTH SPECIFIC PRODRUGS CLAIMED AND THINGS THAT ARE NOT PRODRUGS CLAIMED. AND THE COMPOUND OF THE INVENTION, THAT REFERS TO WHAT IS CLAIMED, THE PRODRUGS OF THE COMPOUND OF THE INVENTION ALSO REFER TO WHAT IS CLAIMED. BUT NEITHER CASE IT IS THE CHEMICAL STRUCTURES THAT THIS PARTICULAR MARKUSH GROUP IDENTIFIES.

SO WE WILL NEXT WEEK EXPLAIN TO YOU HOW WHEN YOU CONSTRUE THIS TERM "ADMINISTERING" YOU ARE TALKING ABOUT ADMINISTERING EITHER A COMPOUND OF THE INVENTION. THAT COULD BE, FOR EXAMPLE, ONE OF THESE MARKUSH GROUPS WITH HERE 5 PRIME, THE OH, AND A LOT OF IT, THE COMPOUNDS -- A LOT OF THE EXAMPLES IN THE PATENT HAVE THAT. I CAN PUT THAT IN A PILL AND GIVE IT TO SOMEBODY.

THIS PATENT DESCRIBES HOW YOU COULD PUT INTO A PILL AND GIVE TO SOMEBODY A COMPOUND OF THE INVENTION THAT HAS THE PHOSPHOROUS ATOM ALREADY PRESENT, OR IT COULD BE A PRODRUG. AND THOSE PRODRUGS, THERE ARE SOME SPECIFICALLY IDENTIFIED, ONE IS CALLED SATE, AND NEXT WEEK I WILL SHOW YOU HOW THE PATENT DESCRIBES THOSE THINGS AND HOW IT IS CLAIMED.

SO IN SHORT, IT IS NOT THE CASE THAT A COMPOUND OF THE

INVENTION IS THE METABOLITE, IT IS WHAT YOU ADMINISTER TO THE PATIENT, IT'S WHAT'S DESCRIBED IN THIS CLAIM. IT CAN BE A PRODRUG, BUT AS I WILL ARGUE NEXT WEEK, ONLY ONE OF THE PRODRUGS THAT PERHAPS CHOSE TO CLAIM, NOT ANY POSSIBILITY OF THE MANY POSSIBILITIES.

DOES YOUR HONOR HAVE ANY QUESTIONS?

THE COURT: NO, BUT I WILL TELL YOU THAT THIS IS VERY HIGH LEVEL FOR MY UNDERSTANDING, SO DON'T HESITATE NEXT WEEK TO GO BACK OVER THIS, BUT THIS IS VERY COMPLICATED FOR ME.

I DON'T KNOW HOW TO PUT THIS IN THE CONTEXT OF THESE BRIEFS, SO THAT IS JUST A LITTLE REQUEST FOR YOU FOR NEXT WEEK.

MR. MCCANN: NO, I UNDERSTAND, YOUR HONOR.

AND REALLY A LOT OF WHAT I WAS TRYING TO DO IS SO NEXT WEEK WHEN I'M SAYING THIS IS A SUBSTITUTION OF THE 5 PRIME POSITION, I THOUGHT IF I WENT THROUGH EXACTLY WHAT THAT MEANT TODAY, IT WOULD HELP YOU UNDERSTAND THE ARGUMENT.

THE COURT: AND IT WILL. AND IT WILL. AND I GREATLY APPRECIATE THAT.

AND I AM NOT UNDERSTANDING HOW MUCH OF THIS CHEMISTRY I'M GOING TO NEED TO UNDERSTAND IN ORDER TO CONSTRUE THE TERM "ADMINISTERING". SO CONCRETE EXAMPLES ARE GOING TO BE VERY IMPORTANT FOR ME, AS YOU COULD SEE WHEN I LATCHED ON TO THE ASPIRIN, AND I OVER SIMPLIFIED IT, AND SOMETIMES I DO THAT JUST TO GIVE YOU A FEEL FOR WHERE I'M TRYING TO KEEP UP. BECAUSE YOU OBVIOUSLY ARE PUTTING A LOT OF TIME INTO THIS AND I WANT TO

RETURN THE RESULTS FOR YOU.

MR. MCCANN: I UNDERSTAND, YOUR HONOR.

AND CERTAINLY NEXT WEEK WE WILL BE VERY FOCUSED ON THAT PORTION OF THE CHEMISTRY THAT PERTAINS TO THE UNDERSTANDING OF "ADMINISTERING".

THE COURT: OKAY. ALL RIGHT. GOOD. NO, I HAVE NO OTHER QUESTIONS. AND I DO APPRECIATE THAT.

ALL RIGHT. MR. RABINOWITZ, DO YOU HAVE ANYTHING ELSE YOU WANTED TO ADD?

MR. RABINOWITZ: NOTHING FURTHER, YOUR HONOR.

I WAS GOING TO ADDRESS SOMETHING. AS YOU SAY, THERE WAS SOME ARGUMENT ABOUT CLAIM CONSTRUCTION, BUT WE WILL RESERVE THAT FOR NEXT WEEK.

THE COURT: AND SOMETIMES IT'S JUST THAT I HAVE SOME THINGS THAT I'M HOPING YOU CAN GIVE ME A CLUE ON, BUT I APPRECIATE YOUR UNDERSTANDING TO MY QUESTIONS.

ALL RIGHT. NEXT WEEK WHEN YOU RETURN, YOU'VE EACH ASKED FOR AN HOUR; IS THAT CORRECT?

MR. MCCANN: THAT WAS THE POSITION IN THE BRIEFING, YOUR HONOR.

WE HAVE LIMITED THINGS DOWN TO THE ONE TERM, SO I THINK THAT WE COULD BEING A LITTLE BIT SHORTER, PERHAPS 45 MINUTES.

MR. RABINOWITZ: I DON'T THINK WE QUITE NEED AN HOUR EACH.

THE COURT: THAT'S FINE. AND I DO APPRECIATE THAT.

I WOULD ASK EACH OF YOU TO MAKE YOUR PRESENTATION UNINTERRUPTED, AND THEN I WOULD GIVE EACH OF YOU A FEW MINUTES TO RESPOND TO WHAT YOU'VE HEARD. SO YOU CAN BE PREPARED FOR THAT AS WELL.

I WON'T BE IN A BIG HURRY, WHEN YOU FIRST WANTED FOUR HOURS I WAS A LITTLE CONCERNED ABOUT MANAGING THAT AMOUNT OF TIME. BUT GIVEN THE WAY IT'S WORKED OUT WITH YOUR AGREEMENT ON THE OTHER TERM, I DO WANT YOU TO BE -- GIVEN THE OPPORTUNITY TO RESPOND TO WHAT EACH OF THE OTHER HAS SAID.

ALL RIGHT. THANK YOU VERY MUCH FOR THIS. I GREATLY APPRECIATE THE TIME AND EFFORT AND DOCTOR, THANK YOU FOR YOUR ASSISTANCE TO THE COURT AS WELL.

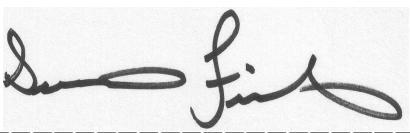
THE COURT: ALL RIGHT. I THINK WE ARE DONE.

(WHEREUPON, THE PROCEEDINGS IN THIS MATTER WERE CONCLUDED.)

CERTIFICATE OF REPORTER

I, THE UNDERSIGNED OFFICIAL COURT REPORTER OF THE UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF CALIFORNIA, 280 SOUTH FIRST STREET, SAN JOSE, CALIFORNIA, DO HEREBY CERTIFY:

THAT THE FOREGOING TRANSCRIPT, CERTIFICATE INCLUSIVE, CONSTITUTES A TRUE, FULL AND CORRECT TRANSCRIPT OF MY SHORTHAND NOTES TAKEN AS SUCH OFFICIAL COURT REPORTER OF THE PROCEEDINGS HEREINBEFORE ENTITLED AND REDUCED BY COMPUTER-AIDED TRANSCRIPTION TO THE BEST OF MY ABILITY.



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SUMMER A. FISHER, CSR, CRR
CERTIFICATE NUMBER 13185 DATED: 3/27/15